REMARKS

Claims 1-4, 13-20, and 23-25 are herein canceled without prejudice to facilitate the prosecution of the remaining claims. In doing so, Applicant reserves the right to purse the canceled subject matter at a later date. Claims 5–9 are amended, and new claims 27-31 are added. Applicant believes that the claims as herein amended patentably distinguish over the teachings of the prior art.

Rejection Under 35 U.S.C. 112

Claim 5 has been amended to specify that the "tumor-selective" expression of a gene is achieved in non-rat cells, and that such a non-rat cell is injected with a gene construct comprising a gene operably linked to a tumor-specific rat Hex II promoter. Support for the proposed claim amendments can be found in Example I of the present application at pages 14 to 16, wherein the *in vivo* success of the claimed method is described and further illustrated in Figs. 6A-6H, and 7A. Consistent amendments are provided for in subsequently dependent claims 6 & 7. Applicant notes that additional support for the subject matter of claim 6 can be found in Example II of the present application (pages 16 – 28) where *in vitro* studies are described using the tumor-selective gene construct of the present invention. Additionally, the Examiner is directed to the teachings of the present application at page 31 lines 12 – 31 wherein the utility of this aspect of the claimed invention is made evident. As such, Applicant respectfully believes that the subject matter of these claims is fully enabled and hereby obviates the Examiner's rejections under 35 U.S.C. 112, first paragraph.

Rejection Under 35 U.S.C. 102(b)

With the cancellation of claims 1-4, and 15 & 18, Applicant respectfully submits that the Examiner's rejections under 35 U.S.C. 102(b) in view of *Mathupala et al.* are herein obviated.

Rejection Under 35 U.S.C. 103(a)

The Examiner has also rejected claims 1-6, 8-20 and 23-25 as obvious under 35 U.S.C. 103(a) in view of previously cited references, including *Mathupala et al.* and *Adams et al.* Of the rejected claims, claims 5, 6 and 8-12 remain in the present application in an amended form, as herein provided. In view of these amendments, Applicant believes that a *prima facie* case of obviousness is not warranted in view of the combination of prior art references as cited by the Examiner. Specifically, Applicant believes that the cited combination of prior art references, including *Mathupala et al.* and *Adams et al*,. do not provide: (1) the invention of the amended claims; nor (2) a suggestion or motivation to combine the prior references in a way so as to achieve the invention of the amended claims (In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 Fed. Cir. 1991). In particular, the combination of prior art references do not teach, suggest or motivate a person of skill in the art to employ a rat HEX II promoter in non-rat tumor cells for the purpose of achieving tumor selective expression of a gene. Although the prior art shows some evidence of a *shift* in the activation of some HEX II isozymes in human tumor cells as compared to human non-tumor cells, Applicant submits that such shifts would not lead a person of ordinary skill in the art to expect that a promoter of such cells would retain properties of tumor-specificity in cells of another species. In fact, Applicant respectfully submits that a shift in "isozyme activation" does not provide a direct correlation to promoter specificity. Accordingly, a person skilled in the art would not have been motivated to arrive at the present invention, nor have expected the claimed invention to work, as shown in the present application, in light of the prior art (In *re* O'Farrell, 853 f.2d 894, 903-904, 7 USPQ2d 1529, 1531 (Fed. Cir. 1988). Furthermore, since the combination of prior art cited by the Examiner does not provide the requisite suggestion and expectation of success of the claimed invention, Applicant respectfully submits that a mere incentive "to try" to achieve the claimed invention would not extend to negate the patentability of the claims as herein provided (In *re* Dow Chem., 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988)).

In support of the above arguments, Applicant respectfully draws the Examiner's attention to the declaration of Dr. Gerald Batist, an inventor in the present application and an expert in the field, as previously submitted in

respect of related application S.N. 09/276,055. Applicant notes that the present application is a continuation-in-part of this related application. As indicated in this declaration (copy enclosed as Exhibit I) Dr. Batist attests to the arguments outlined above, and further emphasizes that the presentation of the results of the claimed invention were received by his peers in the scientific community with interest and surprise. Thus, further supporting the fact that the prior art does not provide "a reasonable expectation of success" for the subject matter of the amended claims. A copy of Dr. Batist's *curriculum vitae*, as previously provided in connection with the above-mentioned declaration is also herein enclosed for the Examiner's convenience.

Although increased levels of a hexokinase type II isoform were noted by *Mathupala et al.* ((1995) in rat tumor cells as compared to rat normal cells, no evidence was presented to indicate that the rat Hex II promoter itself, retained cross-species tumor selectivity. *Mathupala et al.* do not teach of the transformation of cells of other species with a construct including the rat Hex II promoter, and accordingly do not teach or suggest that a rat Hex II promoter is selectively activated in tumor cells in general. In fact, *Mathupala et al.* do not even suggest that a difference in the regulation of hexokinase genes between normal and tumor cells, would be expected in any species other than rat.

Adams et al. disclose "a shift" in hexokinase isoenzyme composition in human renal carcinomas as compared to normal kidney tissue. This reference only goes so far as to suggest that this "isoenzyme shift" may serve as a diagnostic marker to discriminate between normal and malignant tissue. There is absolutely no suggestion in this reference of a HEX II promoter having tumor-selective expression, let alone suggestion of the use of a tumor-specific rat HEX II promoter to achieve tumor-selective expression in non-rat tumor cells. In fact, in column 2 on page 56 of the Adams et al. reference it states:

> "Our results clearly demonstrate that the described reverse transcription followed by multiplex PCT is a fast, reliable and sensitive approach to determine the relative proportion of the individual HK isoenzymes. Our method is useful for detecting a probable shift in isoenzyme mRNA composition, but it does not say anything about the absolute amounts of the individual transcripts."

Applicant respectfully submits that this teaching points to the "unpredictability" of the findings of Adams et al. and does not provide any expectation for the success of the invention as claimed.

New claims 26 to 31 are herein provided to claim an *in vitro* method of screening for tumor-selective expression of a gene. The subject matter of this new claim set was previously encompassed by original claim 5. Applicant points out that the scope of new claim 26 closely aligns with that of original claim 5, while being limited to tumor-selective expression of the rat Hex II promoter in non-rat tumor cells *in vitro* so as to adequately cover those *in vitro* applications of the present invention whereby a gene construct comprising a rat Hex II promoter is inserted into a non-rat cell. Applicant maintains that an *in vitro* method of screening claim of this scope is fairly defined and supported in accordance with the teachings of the present application. The Examiner's attention is once again directed to the teachings of Example II of the present application, and in particular to the teachings of page 22, lines 11 to 20, for support for this aspect of the invention. Furthermore, Applicant submits that these claims are supported with respect to the utility of this subject matter as described on page 31, lines 12 to 31.

In conclusion, Applicant respectfully submits that the present invention provides a new and unobvious method for tumor-selective expression of a gene in a non-rat cell, comprising a gene construct having a rat Hex II promoter that is selectively activated in non-rat tumor cells as compared to normal cells. Accordingly, Applicant believes that the present invention patentably distinguishes over the teachings of the prior art, is fully enabled by the teachings of the specification and is deserving of patentable merit commensurate with the scope of the claims presently on file.

Favourable reconsideration of the Examiner's rejections in this regard is respectfully requested.

Pages showing changes to the above-noted claims set forth above are attached hereto.

Respectfully submitted,

By: _____

David S. Resnick, Reg. No. 34,235
Agent of Record
(Docket No. 701826-50008)

Date: September 4, 2003

Address: NIXON PEABODY, LLP
101 Federal Street
Boston, MA 02110-1000
U. S. A.
Tel.(617) 345-1000